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Applying robust control theory to solve problems in bio-medical sciences: study of an apoptotic model

M Trujillo [1], **V M Becerra and S Hadjiloucas**
School of Systems Engineering, University of Reading, RG6 6AY, UK

E-mail: s.hadjiloucas@reading.ac.uk

Abstract. Biological models of an apoptotic process are studied using models describing a system of differential equations derived from reaction kinetics information. The mathematical model is re-formulated in a state-space robust control theory framework where parametric and dynamic uncertainty can be modelled to account for variations naturally occurring in biological processes. We propose to handle the nonlinearities using neural networks.

1. Introduction

Robust control theory has been considered as a tool in the biomedical community for model validation, optimal experiment design for hypothesis testing, systems oriented drug design, target identification, or multi-target drug dosage optimization. Unfortunately practical application of this method is limited to models that can be linearized without substantial loss of quantitative or qualitative features. Since most problems arising in biomedical applications do not fall in this category, we present a different perspective where traditional parameter sensitivity analysis is translated into sensitivity of biological features that can be measured experimentally. In this study, biological models of an apoptotic process are studied using models describing a system of differential equations derived from reaction kinetics information. The mathematical model is re-formulated in a state-space robust control theory framework where parametric and dynamic uncertainty can be modelled to account for variations naturally occurring in biological processes. Since the standard robust control theory framework is valid for linear systems only, we re-formulate the problem as piecewise linear allowing for specific non-linearities. We propose to handle the nonlinearities using neural networks. The approach overcomes the limitations imposed by forced linearization and extends the applicability of robust control theory to problems encountered within the Bio-medical community.

2. Apoptosis model

Apoptosis is the programed death that regulates the disposal of cells that have been damaged or are no longer required by an organism. Mis-regulation of this process can lead to pathological conditions such as cancer when cells do not die or Alzheimer's condition where cells die more than needed. Many models of apoptosis are available in the literature and choosing an adequate model can be a difficult process. The current study focuses on the EARM (Extrinsic Apoptosis Reaction Model) described in [1] because in the process of creating, evaluating, calibrating and evolving this model, as

[1] To whom any correspondence should be addressed.

this is now broadly accepted in the literature as a comprehensive one, where the associated experimental parameters are well calibrated. Furthermore, the model incorporates the latest hypotheses associated to the different reaction mechanisms postulated in the literature.

The model of the extrinsic apoptotic pathway published in [1] is formed by four sub-circuits that interact. These describe the entire pathway leading to the apoptotic process. The first circuit starts by the addition of tumor necrosis factor (TNF). The TNF-related apoptosis-inducing ligand (TRAIL), binds to its receptor forming the death-inducing signalling complexes (DISC) and activating pro caspase 8 (pro-C8). The second circuit represents the activation of pro-C8 produces caspase 8 (C8). C8 directly activates caspase-3 (C3) which is responsible for the cleavage of Poly (ADP-ribose) polymerase (PARP), an essential cell substrate for cell survival. The third circuit is a feed-forward loop where C8 promotes the cleavage of Bid to form tBid which activates Bax. Activated Bax promotes the formation of pores in the mitochondria to translocate Smac and cytochrome c (CyC) to the cytosol. Smac binds to X-linked IAP (XIAP) preventing it from inhibiting C3. CyC binds to Apaf and then attracts caspase 9 (C9) to form the apoptosome which in turn produces more C3. The fourth circuit is a feedback loop where the production of C3 activates caspase 6 (C6) to produce more C8.

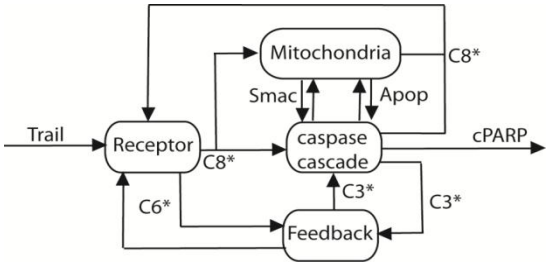

Figure 1. Simplified block diagram of the apoptosis model divided in four sub-circuits. The input is the death inducing ligand TRAIL and the output is the amount of cleaved PARP. The four blocks are the receptor complex, mitochondria, caspace cascade and feedback.

The model has 18 species with non-zero initial conditions and 40 additional species that represent modified forms of the initial 18 species (cleaved and short-lived intermediate species). When these species have moved across membranes, they are annotated differently. All species interact via 28 biochemical reactions that use 70 rate reactions including forward, reverse and catalytic rates for each reaction. The biochemical reactions were then translated into 58 ordinary differential equations.

It has been proposed and experimentally tested by the authors of the model that the apoptotic network works as a variable delay snap-action switch described by the following function:

$$c(t) = f - f\left[1 + e^{\frac{(t-T_d)}{4T_s}}\right]^{-1} \quad (1)$$

where c is the amount of substrate cleaved at time t, f is the fraction cleaved at the end of the reaction, T_d is the delay between TRAIL addition and half the total substrate cleaved (cPARP) and T_s is the switching time between initial and total effector caspase cleavage. This concept is illustrated with the response of cPARP for an initial concentration of TRAIL (Figure 2a).

The authors of the model found that T_d depends on TRAIL dose, but T_s and f are independent of TRAIL dose. The model parameters were calibrated to follow experimental values of T_d, T_s and f. The cell is destined to die when 10% of the total amount of PARP is cleaved therefore, the value of cPARP = 0.1 PARP is the threshold necessary for cell death (Figure 2b). Experiments with TRIAL doses from 2 to 1,000 ng/ml corresponded to a variation in T_d from 140 to 660 minutes. We assume that reducing the TRIAL dose enough to prevent reaching the cPARP threshold will create a cell survival steady

state for long enough to compare the set of parameter values key for differentiating death and survival states. In figure 2b four species are shown as representative of the different stages of the apoptotic process. The initiator caspase C8* is the only concentration that has a slow increment during the delay period Td followed by a sudden increment after reaching the switching time T_s.

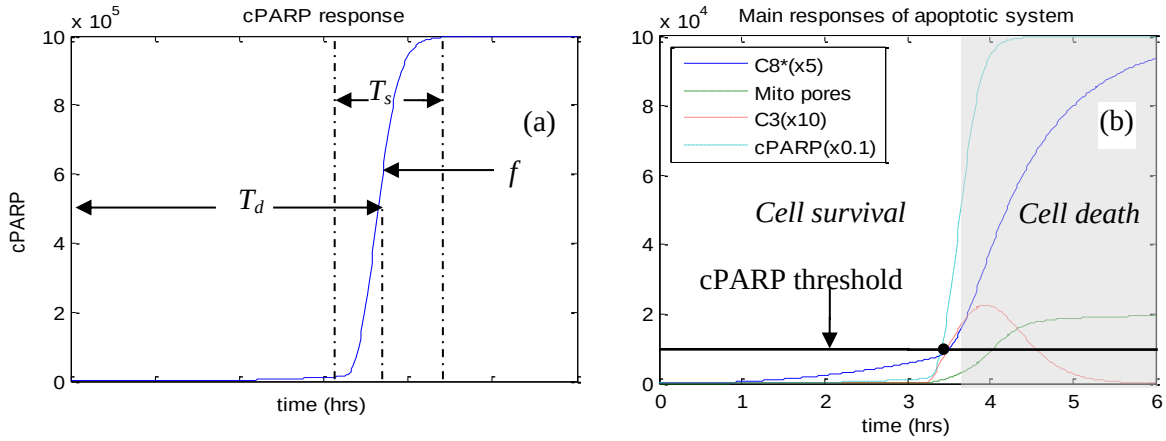

Figure 2. a) cPARP trajectory in response to ligand treatment as described in (1), b) main responses of apoptotic system species; initiator caspaces, mitochondria pores, effector caspaces and cleaved PARP.

3. Nonlinear robust control approach

The most obvious application of robust control for the apoptosis network is to specify desirable behaviour, translate it as performance functions, define boundaries for uncertain parameters and dynamics and design a controller that achieves the required performance for all the possible uncertain scenarios. However, the apoptosis pathway is not yet fully understood, many contradicting models describe different possible hypotheses and experimental data cannot be yet generated to test them. The model we selected has gone through various iterations of modelling, experimental data fitting and calibration but since the experimental measurements of variables in individual cells destroy the cell, it is not possible yet to monitor the same cell through all its stages in the process from reception of the apoptosis-inducing ligand to cell death. Hence we focus in the use of robust control to provide further understanding of the process, before we could design controllers to intervene at the cellular level.

3.1. General robust control problem

Almost any dynamical system can be put in the general form described in figure 3a. In this general form P is a plant consisting of the nominal dynamics of our system augmented with performance functions defined by the user to force the system to satisfy design requirements, K is the controller to be designed to satisfy performance and stability requirements for all the systems resulting from the combination of the plant P with the uncertain block Δ which contains the allowed variations in parameter space and un-modelled dynamics that may affect the system. w is a vector of the external inputs to the system, z are the outputs to be controlled, u are the inputs to the controller, y are the measurements available from the system, w_p and z_p are the output and input to the uncertainty block.

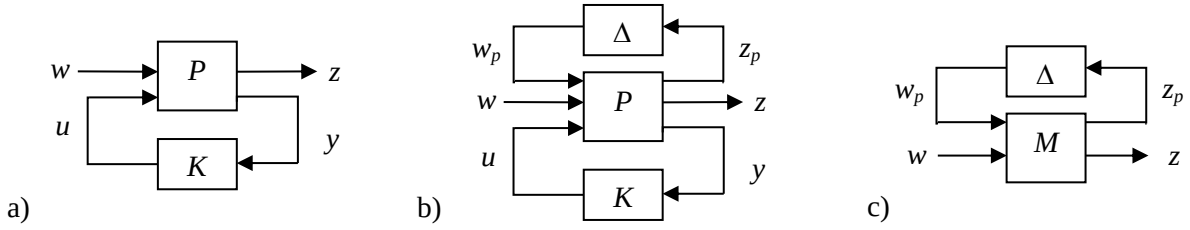

Figure 3. a) General plant P and controller K, b) Robust control problem for uncertainty Δ, c) Plant and controller integrated in M for the analysis of robust performance

The mathematical representation of the perturbed plant *P* is given by

$$P:\begin{cases}\dot{x} = f(x) + g_1(x)w + g_2(x)u;\ \ x(t_0) = x_0\\ y = x\\ z = h_1(x) + k_{12}(x)u\end{cases} \tag{2}$$

where *x* is the state vector of the nominal system, $f(x)$ are the dynamics of the system as described in the nominal model, $g_1, g_2, h_1, h_2, k_{12}$ and k_{21} are functions of *x*. The nonlinear H_∞ problem is to find a controller action *u* that results in an $\mathcal{L}_2$-gain of the system P from *w* to *z* less or equal to a given γ while maintaining system stability. This is an optimisation problem where the allowed disturbance has to be maximized while the control energy has to be minimized. Solutions to this problem come from theories such as differential games, disipativity, viscosity among others. The final result is a Hamilton-Jacobi-Isaacs equation (HJIE) of the form:

$$V_x(x)f(x) + \frac{1}{2}V_x(x)\left[\frac{1}{\gamma^2}g_1(x)g_1^T(x) - g_2(x)g_2^T(x)\right]V_x^T(x) + \frac{1}{2}h_1^T(x)h_1(x) = 0, V(0) = 0 \tag{3}$$

Finding a storage function $V_x(x)$ that satisfies the HJI in most cases is not straightforward. Once a function $V_x(x)$ satisfying equation 3 is found, the minimum energy control and the maximum disturbance allowed for the system in figure 3 a) are given by:

$$u(x) = \alpha(x) = -g_2^T(x)V_x^T(x), \qquad w(x) = \frac{1}{\gamma^2}g_1^T(x)V_x^T(x) \tag{4}$$

For the system given in figure 3 b) the perturbed plant P_Δ becomes

$$P_\Delta:\begin{cases}\dot{x} = f(x) + \Delta f(x,\theta,t) + g_1(x)w + [g_2(x) + \Delta g_2(x,\theta,t)]u;\ \ x(t_0) = x_0\\ y = [h_2(x) + \Delta h_2(x,\theta,t)] + k_{21}(x)w\\ z = h_1(x) + k_{12}(x)u\end{cases} \tag{5}$$

where $\Delta f, \Delta h_2$ and Δg_2 are unknown functions that belong to the set of admissible uncertainties and θ are the system parameters that may vary over time in a defined range [2].

For the purpose of this paper, we are not concerned with the design of a controller since we consider the apoptosis network as a whole system with an integrated controller. Figure 3b shows the general framework used in robust control theory for analysis rather than synthesis where *P* and *K* form a single block *M*. This framework allows us to ask how big can the perturbation be and still permit the system to achieve the desired performance. Then, by manipulating the weighting functions (performance criteria) and the allowed uncertainties we can perform sensitivity analysis to measure the impact of various parameters in the system, test different hypothesis for model validation/invalidation and identify underlying mechanisms and interactions between species of the system.

3.2. Performance functions, modeling uncertainty and solving the HJIE with Neural networks

The performance functions are used to modify the nominal system to include desired trajectories. In the case of the apoptosis network, it was suggested in [3] that four features of the time trajectories from cytosolic Smac and cPARP could define the difference between a normal and a pathological response. These are: 1) t_{PARP} which is the time it takes 50% of PARP to be cleaved, 2) t_{MOMP} which is the time it takes for half the Smac to translocate from the mitochondria, 3) t_{switch} which is the time between the start and finish of PARP cleavage and 4) f_{PARP} which is the amount of PARP cleaved after the experiment or simulation. It is possible then to identify values of interest for these features and define performance functions accordingly. By defining structural perturbations on various species we

can identify which once affect the most each feature. To study the effects that variations in the system have on the defined features of interest we have to model such variations as uncertainties Δ and incorporate them in the system *M*. Parametric uncertainty is the variation in parameter space that we want to explore and dynamic uncertainty accounts for the unknown dynamics taking place in the system. When a mixture of both uncertainty types has to be analyzed then Δ becomes a structured uncertainty block that can be separated from the plant as in figure 3b. A solution for the HJIE from equation 3 can be found indirectly by using iterative processes. The HJI is broken in a sequence of linear partial differential equations and the aim becomes finding a possible storage function $V_x(x)$. In each iteration step, the performance of an initial stabilizing controller is improved until a satisfactory solution to the HJI is found through several iterations. Even though finding $V_x(x)$ for the linear partial differential equations at each iteration is less complicated than finding it for the HJIE, nevertheless, it is still a difficult task that needs to be solved. One possible way is by approximating $V_x(x)$ with a neural network at each iteration. A more complete description of the process can be found in [4].

4. Conclusion

So far, because of its implementation complexity, robust control theory has failed to gain popularity as a tool in the bio-medical field. Non-linear robust control theory is still under development and soft computing alternatives are constantly introduced to overcome the complexity of solving problems that cannot be tackled by linearization. The HJIE approach should be seen as an extension to linear $\mathcal{H}\infty$-control theory, providing a unifying approach in treating disturbances using a nonlinear counterpart of the Riccati equations which are conventionally used to solve linear problems. Different soft computing methodologies such as neural networks and fuzzy systems theory are worthwhile exploring to overcome the difficulties of solving nonlinear HJI equations. A particular advantage in the general formulation developed for the apoptotic process described in section 3.1 is that it clarifies the parameters that need to be estimated (for example the different uncertainties introduced in the model and their inter-relationship to other biochemical pathways).

Furthermore, because of the nice stability and stabilizability properties of passive systems, such as (global) asymptotic stabilizability by pure-gain output-feedback it is considerably desirable in pharmacological or radiological intervention to render the associated biochemical non-linear systems passive. In non-linear control theory, it is well understood that if the state space of a system is reachable from the origin x=0, by an appropriate choice of an input $u(t)$ so that its output is finite, then it can be rendered dissipative. A further goal of the proposed formulation is, therefore, to identify the control points in biochemical reactions that would render interconnected pathways passive through the control of the supply rate (in our case the cPARP threshold in Fig. 2). Since most biochemical pathways can be seen as interconnected dissipative sub-systems of processes described by storage functions, the approach should have a wide domain of applications across Systems Biology. The present work, therefore, serves also as an intellectual scaffolding upon which other Systems-Biology problems can be formulated where seemingly non-linear processes can be controlled though the control of the supply rate to an identified storage function of the system.

References

[1] Albeck J G, Burke J M, Spencer S L, Lauffenburger D A and Sorger P K 2008 *PLoS Biology*, **6**(12): e299.
[2] Abu-Khalaf M, Huang J and Lewis F L 2006 *Nonlinear H2/H∞ Constrained Feedback Control* (Springer-Verlag London)
[3] Gaudet S, Spencer S L, Chen W W, Sorger P K, 2012, *PLoS Computational Biology*, 1-15
[4] Aliyu M D S 2011 *Nonlinear H∞-control, Hamiltonian systems and Hamilton-Jacobi equation* (CRC Press, Taylor &Francis, Boca Raton FL, USA)